2024 ASCO® ANNUAL MEETING

# ReNeu: A Pivotal Phase 2b Trial of Mirdametinib in Adults and Children with Neurofibromatosis Type 1 (NF1)-Associated Symptomatic Inoperable Plexiform Neurofibroma (PN)

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# Background and Conclusions

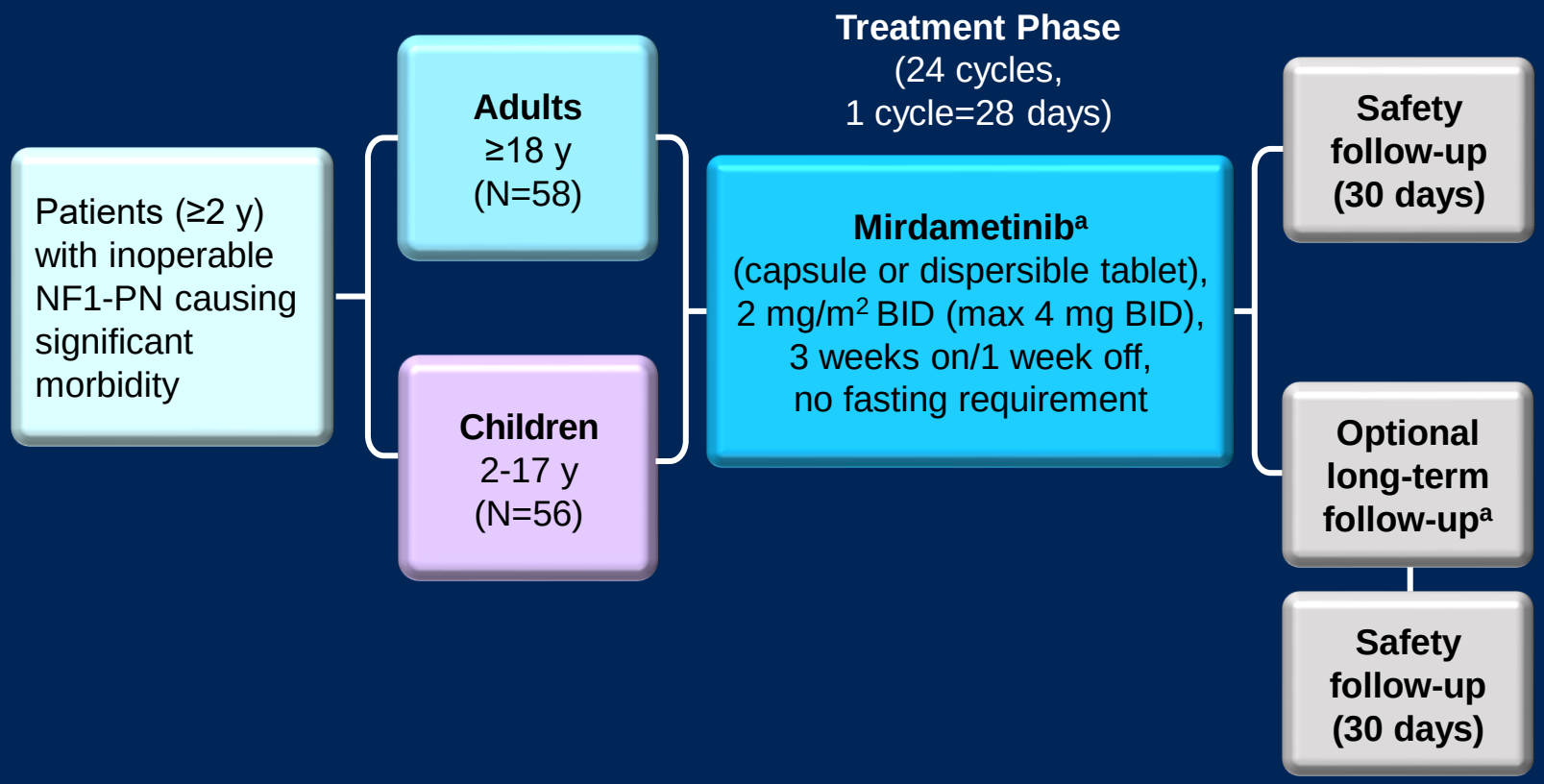
- Plexiform neurofibromas (PN) are non-malignant nerve sheath tumors present in 30%-50% of patients with neurofibromatosis type 1 (NF1)[1,2]
  - PN often cause morbidities, including pain, impaired HRQoL, disfigurement, and increased risk of malignant transformation[3,4]
- No pharmacologic therapies are approved for adults; one MEK inhibitor is FDA approved for children (≥2 years)[5]
- Mirdametinib is an investigational, oral, highly selective, CNS-penetrant, small-molecule MEK1/2 inhibitor[a]
  - A phase 2 trial (NF106) of mirdametinib demonstrated efficacy and a manageable safety profile in adults and adolescents (≥16 years) with NF1-PN[6]

**In ReNeu, mirdametinib demonstrated deep and sustained tumor volume reductions and improvement in patient (and parent proxy) reported pain and HRQoL and a manageable safety profile in adults and children**

[a]Mirdametinib is an investigational product that has not been approved by any regulatory authority; the safety and efficacy of mirdametinib have not been established.
CNS, central nervous system; FDA, US Food and Drug Administration; HRQoL, health-related quality of life; MEK1/2, mitogen-activated protein kinase kinase 1/2; NF1, neurofibromatosis type 1; PN, plexiform neurofibromas.
1. Prada CE, et al. *J Pediatr*. 2012;160:461-467. 2. Miller DT, et al. *Pediatrics*. 2019;143:e20190660. 3. Gutmann DH, et al. *Nat Rev Dis Primers*. 2017;3:17004. 4. Fisher MJ, et al. *Neuro Oncol*. 2022; 24:1827-1844.
5. KOSELUGO [Prescribing Information]. AstraZeneca Pharmaceuticals LP; 2024. 6. Weiss BD, et al. *J Clin Oncol*. 2021;39(7):797-806.

# ReNeu: A Multicenter, Open-label, Pivotal Phase 2b Trial of Mirdametinib in Adults and Children with NF1-PN (NCT03962543)






**Primary Endpoint**

- Confirmed ORR (% of patients with ≥20% reduction in target tumor volume by MRI on consecutive scans assessed by BICR)[b]

**Key Secondary Endpoints**

- DOR
- PROs from BL to Cycle 13:
  - Pain severity (NRS-11)
  - HRQoL (PedsQL)
- Safety and tolerability

[a]In the LTFU, patients continue on mirdametinib at the last dose assigned in the treatment phase. [b]Per REiNS criteria. Primary endpoint assessed in 24-cycle treatment phase.
BICR, blinded independent central review; BID, twice a day; BL, baseline; DOR, duration of response; LTFU, long-term follow-up phase; NRS-11, Numeric Rating Scale-11; ORR, objective response rate; PedsQL, Pediatric Quality of Life Inventory; PRO, patient-reported outcomes; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis.

1. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT03962543. Accessed May 9, 2024.

# Baseline Demographics and Characteristics

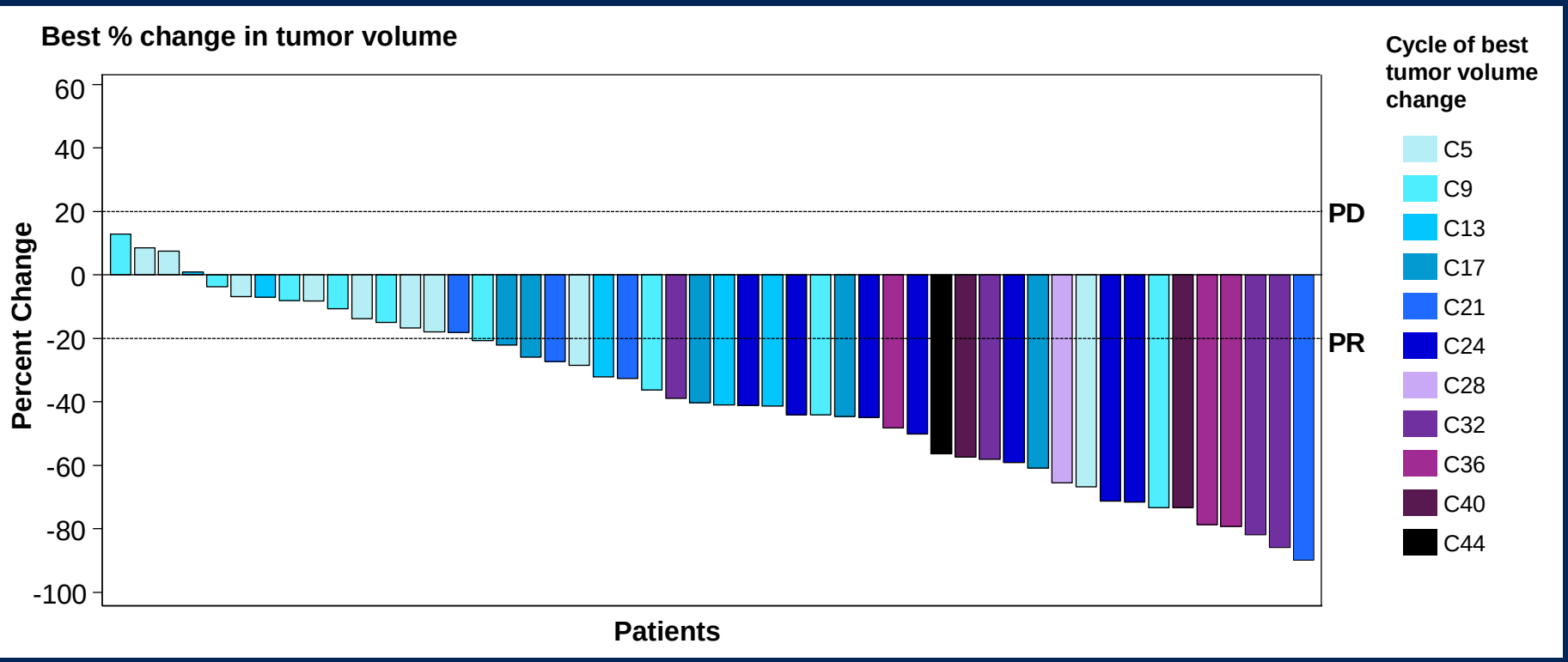


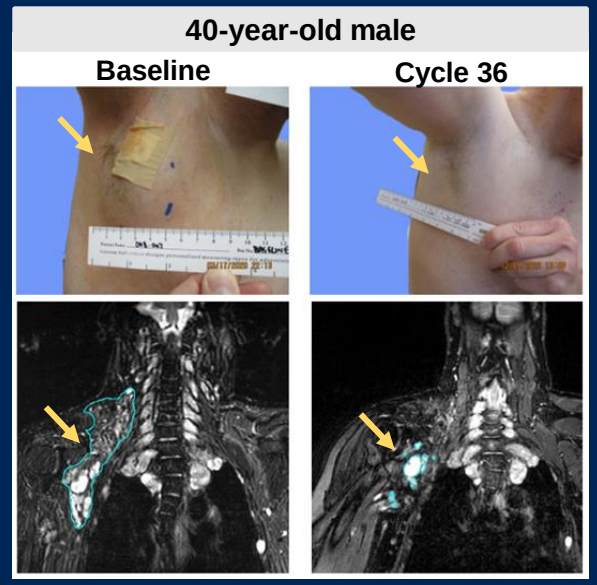
| | Adults (N=58) | Children (N=56) |
|---|---|---|
| **Age, median (range), years** | **34 (18 to 69)** | **10 (2 to 17)** |
| **Sex, n (%)** | | |
| Female | 37 (64) | 30 (54) |
| Male | 21 (36) | 26 (46) |
| **Volume of target PN, median (range), mL** | **196 (1 to 3457)** | **99 (5 to 3630)** |
| **Target PN progressing at trial entry, n (%)** | **31 (53)** | **35 (62)** |
| **Location of target PN, n (%)** | | |
| Head and neck | 28 (48) | 28 (50) |
| Lower/upper extremities | 17 (29) | 8 (14) |
| Paraspinal | 5 (9) | 4 (7) |
| Torso[a] | 5 (9) | 8 (14) |
| Other | 3 (5) | 8 (14) |
| **Type of PN-related morbidity, n (%)** | | |
| Pain | 52 (90) | 39 (70) |
| Disfigurement or major deformity | 30 (52) | 28 (50) |
| Motor dysfunction/weakness | 23 (40) | 15 (27) |
| Airway dysfunction | 3 (5) | 7 (12) |
| Other | 10 (17) | 12 (21) |

[a]Includes chest wall, mesentery and pelvis, and abdominal wall.

# Mirdametinib Demonstrated Significant ORR by BICR and Deep and Durable Tumor Volume Reductions in Adults





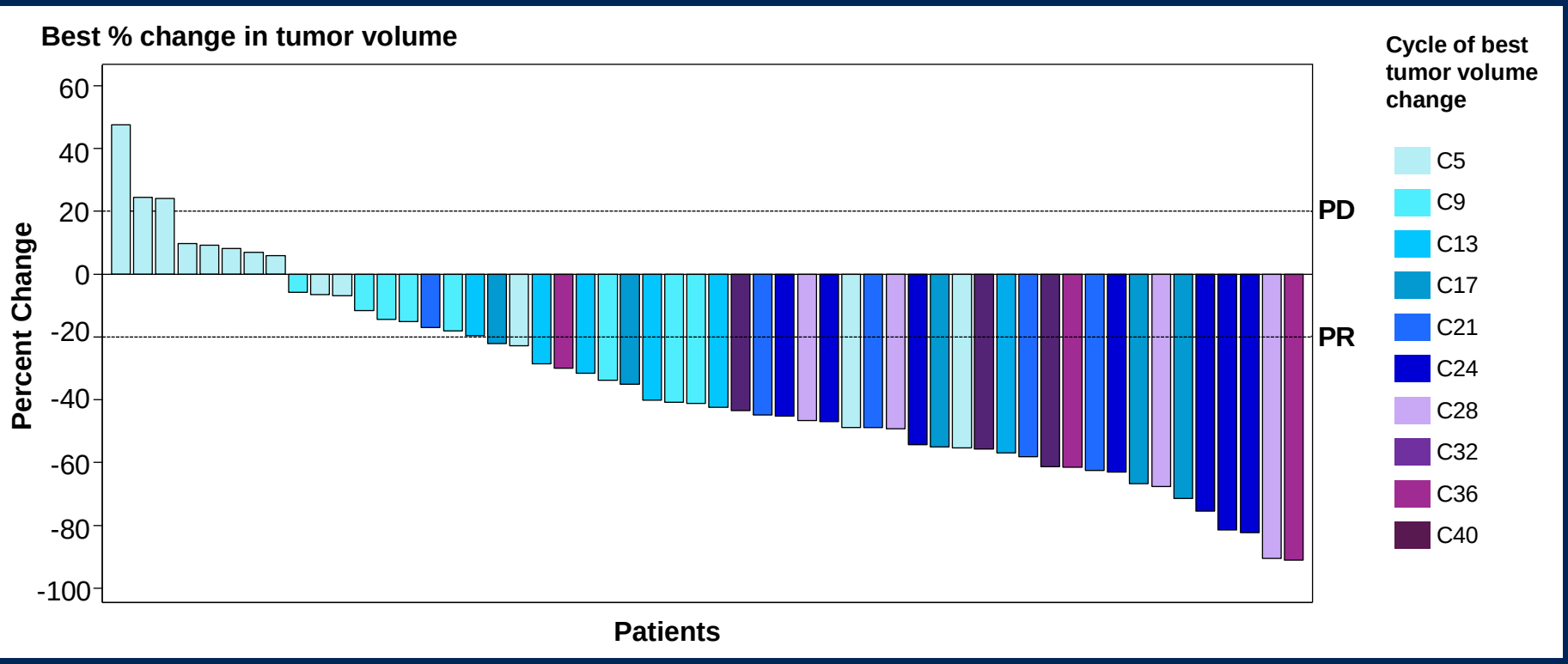

Target PN volume change from baseline at Cycle 36: –79%

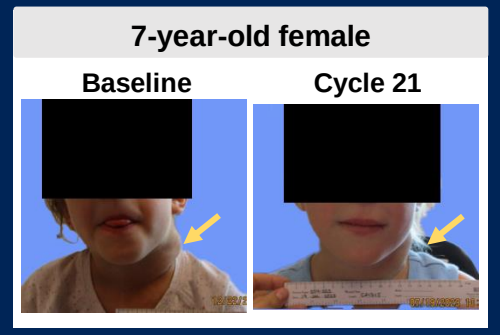
- Confirmed ORR: 41%[a] (24/58; *P*<.001 vs null hypothesis[b])
  - Two additional adults achieved a confirmed PR in the LTFU
- Median best change in tumor volume: –41% (range, –90 to 13)
- 62% of adults with confirmed objective response achieved a deep response (>50% tumor volume reduction)
- Median DOT: 22 months
- Median time to onset of response: 7.8 months (range, 4 to 19)
- Median DOR: not reached

[a]Confirmed ORR defined as proportion of patients with ≥20% reduction of target PN volume from baseline assessed by BICR on ≥2 consecutive scans within 2 to 6 months during the treatment phase. [b]The minimum clinically relevant ORR (null) was defined as 23% for adults.
DOT, duration of treatment; PD, progressive disease; PR, partial response.

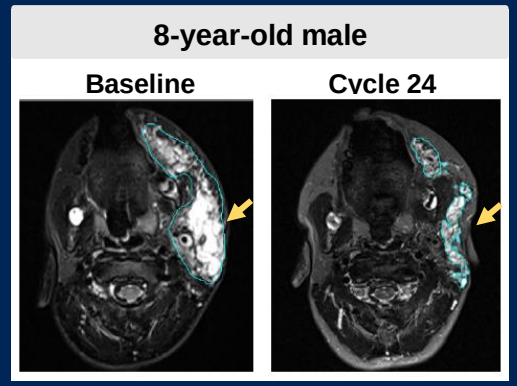
# Mirdametinib Demonstrated Significant ORR by BICR and Deep and Durable Tumor Volume Reductions in Children






Target PN volume change from BL at Cycle 21: –49%




Target PN volume change from BL at Cycle 24: –82%

- Confirmed ORR: 52%[a] (29/56; *P*<.001 vs null hypothesis[b])
  - An additional child achieved a confirmed PR in the LTFU
- Median (range) best change in tumor volume: –42% (–91 to 48)
- 52% of children with confirmed objective response achieved a deep response (>50% tumor volume reduction)

- Median DOT: 22 months
- Median time to onset of response: 7.9 months (range, 4 to 19)
- Median DOR: not reached

[a]Confirmed ORR defined as proportion of patients with ≥20% reduction of target PN volume from baseline assessed by BICR on ≥2 consecutive scans within 2 to 6 months during the treatment phase. [b]The minimum clinically relevant ORR (null) was defined as 20% for children.

# Mirdametinib Treatment Demonstrated Improvements in Pain and HRQoL

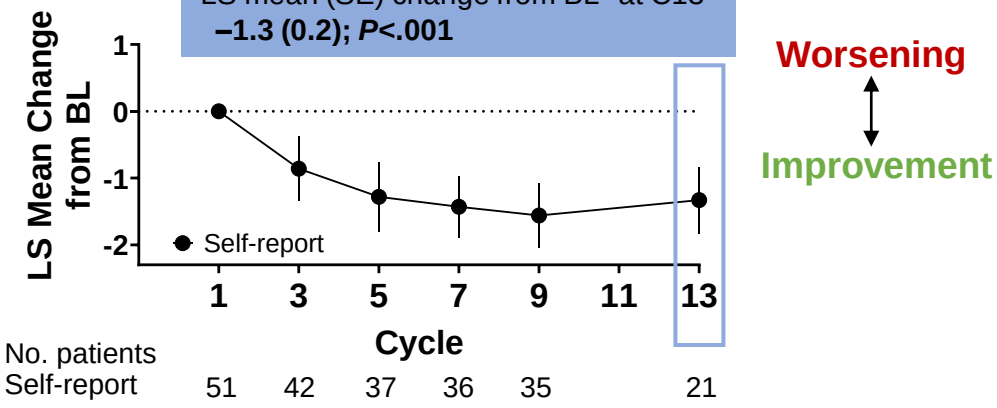


**Worst tumor pain** ***(NRS-11 score)***

**HRQoL** ***(PedsQL Total Score)***

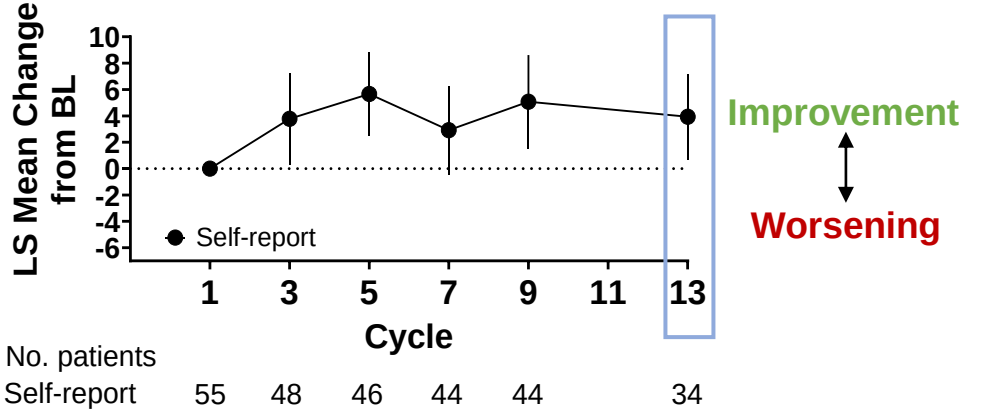
## ADULTS (N=58)

LS mean (SE) change from BL[a] at C13
**–1.3 (0.2); *P*<.001**




| No. patients | | | | | | |
|---|---|---|---|---|---|---|
| Self-report | 51 | 42 | 37 | 36 | 35 | 21 |

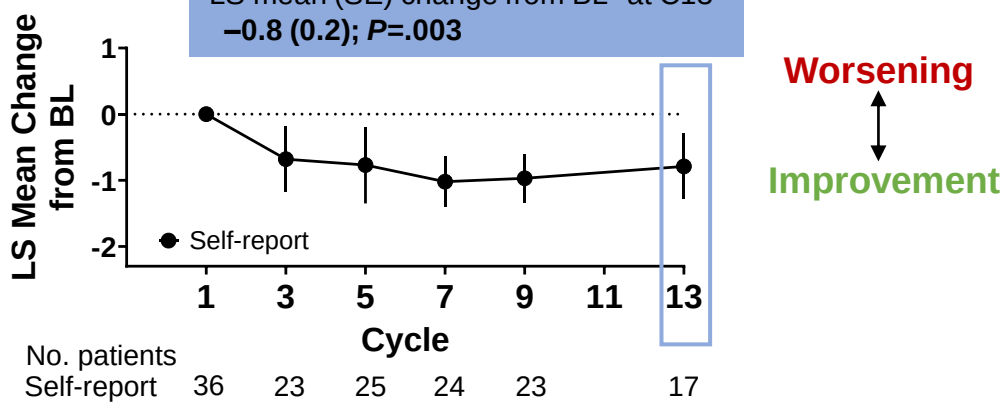
LS mean (SE) change from BL[a] at C13
**3.9 (1.6); *P*=.018**




| No. patients | | | | | | |
|---|---|---|---|---|---|---|
| Self-report | 55 | 48 | 46 | 44 | 44 | 34 |

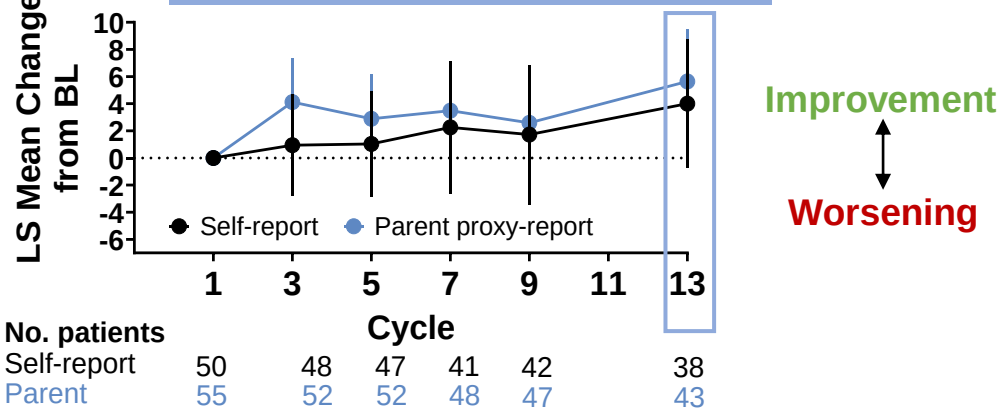
## CHILDREN (N=56)

LS mean (SE) change from BL[a] at C13
**–0.8 (0.2); *P*=.003**




| No. patients | | | | | | |
|---|---|---|---|---|---|---|
| Self-report | 36 | 23 | 25 | 24 | 23 | 17 |

LS mean (SE) change from BL[a] at C13
**4.0 (2.4); *P*=.096 (self-report)**
**5.6 (1.9); *P*=.005 (parent proxy-report)**




| No. patients | | | | | | |
|---|---|---|---|---|---|---|
| Self-report | 50 | 48 | 47 | 41 | 42 | 38 |
| Parent proxy-report | 55 | 52 | 52 | 48 | 47 | 43 |

[a]BL was Cycle 1, Day 1.
LS, least-squares; SE, standard error.

# Mirdametinib Safety Profile

| Treatment-related adverse events (TRAEs) | Adults (N=58)[a] | | Children (N=56) | |
|---|---|---|---|---|
| Safety population, n (%) | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Any TRAE** | **57 (98)** | **9 (16)** | **53 (95)** | **14 (25)** |
| **TRAEs of any grade reported in ≥20% of patients in either cohort** | | | | |
| Dermatitis acneiform | 45 (78) | 5 (9) | 24 (43) | 1 (2) |
| Diarrhea | 28 (48) | 0 (0) | 21 (38) | 1 (2) |
| Nausea | 21 (36) | 0 (0) | 12 (21) | 0 (0) |
| Vomiting | 16 (28) | 0 (0) | 8 (14) | 0 (0) |
| Fatigue | 12 (21) | 1 (2) | 5 (9) | 0 (0) |
| Ejection fraction decreased | 7 (12) | 0 (0) | 11 (20) | 1 (2) |
| Blood creatinine phosphokinase increased | 6 (10) | 1 (2) | 11 (20) | 4 (7) |
| Paronychia | 1 (2) | 0 (0) | 17 (30) | 0 (0) |
| **Serious TRAEs[b]** | 1 (2) | | 0 (0) | |
| **Interruptions due to TRAEs** | 5 (9) | | 8 (14) | |
| **Dose reductions due to TRAEs** | 10 (17) | | 7 (12) | |
| **Discontinuations due to TRAEs[c]** | 12 (21) | | 5 (9) | |

[a]There was one death due to Covid-19 in an adult (not considered to be treatment-related). [b]One treatment-related SAE in adult cohort, grade 3 RVO with confounding factors (hormonal contraception and Covid-19 vaccination). No treatment-related SAEs or RVO in pediatric cohort. [c]TRAEs leading to treatment discontinuation in >1 patient included dermatitis acneiform (4 adults, 1 child), diarrhea (4 adults, 1 child), nausea (4 adults), rash (1 adult, 1 child), and urticaria (2 children). The presence of more than 1 AE may have led to treatment discontinuation in a patient.
SAE, serious adverse event; RVO, retinal vein occlusion; TRAE, treatment-related adverse event.

# Key Takeaways

- Largest multicenter NF1-PN trial to date, prospectively utilized BICR to confirm target tumor response
- Primary endpoint of confirmed ORR (per REiNS criteria) 41% in adults and 52% in children, median DOR not reached
  - An additional 2 adults and 1 child achieved a confirmed response in the long-term follow-up phase
- Largest percentage reduction in target PN volume published in clinical trials of targeted agents[1-6]
- Improvement in pain severity (NRS-11) and HRQoL (PedsQL) from baseline
- Manageable safety profile, majority of TRAEs were grade 1/2
  - Rates of interruptions, reductions, and common MEK inhibitor-related AEs were lower vs previously published phase 2 MEK inhibitor studies in pediatric NF1-PN[1,2,7,a]
- Dispersible tablet formulation for children and adults with difficulty swallowing, and no fasting requirement

**Mirdametinib demonstrated deep and sustained tumor volume reductions and improvement in patient (and parent proxy) reported pain and HRQoL in adults and children**

[a]No head-to-head studies have been conducted between mirdametinib and other MEK inhibitors.

AEs, adverse events; BICR, blinded independent central review; DOR, duration of response; HRQoL, health-related quality-of-life; MEK, mitogen-activated protein kinase kinase; NF1-PN, neurofibromatosis type 1 plexiform neurofibroma; NRS-11, Numeric Rating Scale-11; ORR, objective response rate; PedsQL, Pediatric Quality of Life Inventory; PN, plexiform neurofibroma; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; TRAEs, treatment-related adverse events.

1. Gross AM, et al. *Neuro Oncol*. 2022;24(11):1978-1988. 2. Gross AM, et al. *N Engl J Med.* 2020;382(15):1430-1442. 3. Gross AM, et al. *Neuro Oncol*. 2023;25(10):1883-1894. 4. Suenobu S, et al. *Neurooncol Adv*. 2023;5(1);vdad054. 5. Dombi E, et al. *N Engl J Med.* 2016;375(26):2550-2560. 6. Fisher MJ, et al. *Nat Med.* 2021;27(1):165-173. 7. KOSELUGO [Prescribing Information]. AstraZeneca Pharmaceuticals LP; 2024.

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